J Anesth (2013) 27:712–719
DOI 10.1007/s00540-013-1617-5

ORIGINAL ARTICLE

Mild hypercapnia with hyperventilation attenuates recovery from anesthesia in elderly patients

Kishiko Nakai · Hitoshi Yoshida · Hiroshi Hashimoto · Tetsuya Kushikata · Futoshi Kimura · Masatou Kitayama · Hironori Ishihara · Kazuyoshi Hirota

Received: 31 January 2013 / Accepted: 11 April 2013 / Published online: 24 April 2013

Abstract
Purpose Mild hypercapnia with hyperventilation has been reported to significantly decrease recovery time from inhaled anesthesia in young and middle-aged patients. However, its efficacy has not yet been clarified in elderly patients, although delayed emergence can deteriorate their quality of recovery.
Methods We enrolled 30 elderly patients (≥65 years) and 30 middle-aged patients (45–64 years) who were scheduled for ophthalmic surgery and allocated them to the control or the device group. Anesthesia was maintained with 1.5 % sevoflurane. Mild hypercapnic hyperventilation was induced by the ANEclear anesthesia recovery device. The primary outcome was the time from vaporizer shut-off to initial response (eye or mouth opening, nodding, or grasping hand) in elderly patients. The secondary outcomes were the time to extubation and leaving the operating room (OR), the time to reach 50 % of the difference between BIS at extubation and vaporizer shut-off (BIS ET_{50}), and interaction between the recovery measures and patient age.
Results The ANEclear significantly reduced the time to initial response, extubation, leaving the OR, and BIS ET_{50} in both age groups: their means and 95 % CI of the ratio of two means ($Mean_{ANEclear}/Mean_{control}$) were 0.576 (0.500, 0.660), 0.595 (0.523, 0.673), 0.713 (0.622, 0.812), and 0.547 (0.444, 0.663), respectively, in the elderly group, and 0.717 (0.591, 0.849), 0.723 (0.609, 0.842), 0.855 (0.736, 0.982), and 0.631 (0.463, 0.813), respectively, in the middle-aged group. The recovery measures were shortened equally in both age groups: *P* values for the interaction were 0.060679, 0.062534, 0.069215, and 0.420061, respectively.
Conclusions Recovery time was significantly decreased by the ANEclear in the elderly group. This reduction was comparable to the time for middle-aged patients.

Keywords Recovery from anesthesia · Sevoflurane · Elderly · Hyperventilation

Introduction

The number of general anesthesia cases in elderly patients is increasing. Aging delays inhaled anesthetic elimination because tissue or blood solubility, and fat compartment content, increase with aging, by which inhaled anesthetic is accumulated in such tissues [1, 2]. In addition, a pharmacokinetic-pharmacodynamic study revealed that the speed of change of sevoflurane effect, shown as effect-site equilibration half-time, becomes slower with aging [3]. All these concerns lead to delayed recovery in elderly patients [2, 3]. Delayed emergence can result in poor quality of recovery, thereby causing prolonged stays in the operating room (OR) or postanesthesia care unit (PACU) [4].

Hyperventilation has been used in combination with both isocapnia and hypercapnia to speed emergence and recovery from inhaled anesthesia by increasing both alveolar ventilation and cerebral blood flow. By adding carbon dioxide (CO_2) to a breathing circuit, the partial pressure of carbon dioxide in the blood ($PaCO_2$) can be maintained

K. Nakai · H. Hashimoto · T. Kushikata · F. Kimura · M. Kitayama · H. Ishihara · K. Hirota
Department of Anesthesiology, Hirosaki University Graduate School of Medicine, Hirosaki, Japan

H. Yoshida (✉)
Department of Emergency and Disaster Medicine, Hirosaki University Graduate School of Medicine, 5 Zaifu-cho, Hirosaki 036-8562, Japan
e-mail: hyoshida@cc.hirosaki-u.ac.jp

during hyperpnea [5]. In the past this required a special system with a CO_2 tank for regulating inspired oxygen and CO_2 concentrations [5, 6]. The ANEclear (Anecare, Salt Lake City, UT, USA), an easy-to-use anesthesia recovery device, was developed to maintain normal to mild hypercapnic levels during hyperpnea to speed recovery from inhaled anesthetics. It has an expandable and contractible rebreathing loop that adds dead space into the breathing circuit, which allows patients to partially rebreathe their expired CO_2, resulting in a controlled rise in the arterial CO_2, while allowing hyperventilation without lowering the arterial CO_2, and while also preventing the rebreathing of inhaled anesthetics through the addition of a gas absorber [7–9]. In previous studies in young and middle-aged patients while using this device, the time between turning off the vaporizer and recovery from anesthesia with isoflurane, sevoflurane, and desflurane was shortened by 52–64 % [8, 9], whereas the effectiveness of this device in elderly patients has not been reported. Hovorka [10] showed that, in both young and old patients, hypocapnia degraded recovery scores to the same degree and that there was a trend to improved recovery scores when increasing levels of CO_2 were used in both groups. Thus, we hypothesized that the use of mild hypercapnia in conjunction with hyperventilation could reduce the recovery time for elderly patients, and that the end effects would be comparable to those for middle-aged patients. In this present study, we investigated whether hypercapnic hyperventilation would be effective for elderly patients and compared its effects in elderly versus middle-aged patients.

Materials and methods

Study population

After obtaining approval from the University Ethical Committee and obtaining signed informed consent from the subjects, 30 elderly patients (≥65 years of age) and 30 middle-aged patients (45–64 years of age) with ASA physical status I or II scheduled for greater than 1 h elective ophthalmic surgery under general anesthesia were enrolled. Patients were randomly assigned to the control or the device in each age-related group. We excluded patients with chronic obstructive pulmonary, neurological, or psychiatric diseases.

Study design

Each patient was premedicated with 4–10 mg oral diazepam 1.5 h before arrival in the OR. The Aestiva/5 (Datex-Ohmeda, GE Healthcare, Buckinghamshire, United Kingdom) anesthesia delivery system was used and the following monitors were applied: pulse oximetry, electrocardiogram, noninvasive blood pressure, body temperature (Life Scope J, BSM-9101; Nihon Kohden, Tokyo, Japan), bispectral index (BIS Model A-2000, version XP; Aspect Medical Systems, Newton, MA, USA), end-tidal CO_2 ($EtCO_2$), inspired oxygen, and inspired and end-tidal sevoflurane concentration (EtSevo) (Multigas Unit AG-920R; Nihon Kohden). Anesthesia was induced with a remifentanil infusion (0.5 μg/kg/min) and propofol (1–2 mg/kg). Tracheal intubation was facilitated with vecuronium bromide (0.08 mg/kg). Anesthesia was maintained with a vaporizer dial setting of sevoflurane at 1.5 % in oxygen and air ($F_IO_2 = 0.4$). A continuous infusion of remifentanil was titrated at 0.05–0.5 μg/kg/min to maintain blood pressure and heart rate within ±20 % of preinduction values. The $EtCO_2$ was kept at 33 mmHg with a respiratory rate of 8–10 breaths/min and a tidal volume of 6–10 ml/kg.

When surgery was completed, the remifentanil infusion was stopped, and the vaporizer was turned off. We adjusted the settings of the anesthesia machine and the ventilator as previously reported by Sakata et al. [9]. The fresh gas flow was increased to 10 l/min. In the treated group, the device was inserted between the endotracheal tube and the breathing circuit "Y" piece with the rebreathing loop fully extended (Fig. 1). The controlled respiratory rate was increased to 16–20 breaths/min and the tidal volume was increased as needed to double the minute ventilation at cessation of sevoflurane. The length of the variable rebreathing loop was adjusted to keep $EtCO_2 \leq 55$ mmHg. In the control group, the respiratory rate and tidal volume were not changed. In each group the patients were loudly verbally prompted to open their eye(s) or mouth, nod, or grasp the investigator's hands every minute after discontinuation of sevoflurane. After responding to one of these commands, the patients were asked to take a deep breath, and their tracheas were extubated when they were able to breathe slowly with good chest wall movement. All patients were transferred from the OR to the PACU when their respiratory rate was >8 breaths/min, their SpO_2 was

Fig. 1 ANEclear

>98 % (O_2 mask, 6 l/min), and their blood pressure and heart rate were maintained within ±20 % of the preinduction value.

Data collection

The following demographic data were collected: gender, age, height, weight. The duration of surgery and anesthesia, which were defined as time from conjunctiva incision to closure, and from induction of anesthesia to extubation, respectively, were recorded. When surgery was finished, the inspired concentration of sevoflurane was recorded. Minute ventilation, BIS, $EtCO_2$, EtSevo, mean arterial pressure, and heart rate were recorded every minute at cessation of sevoflurane inhalation until patient extubation. Recovery time was measured from the time of turning off the vaporizer to the following three events: the patient's initial response, tracheal extubation, and leaving the OR. Initial response was defined as the patient's first correct response to either open their eye(s) or mouth, nod, or grasp the investigator's hands. The anesthesiologist who recorded the time to these events was not blinded to the use of the device. The following perioperative complications were also recorded in the PACU as present or absent: postoperative nausea, postoperative vomiting, shivering, agitation/delirium defined as restlessness/excitement, and hypoxemia ($SpO_2 < 90$ %).

Statistical analysis

The primary objective was to determine whether the anesthesia recovery device reduced recovery time from sevoflurane anesthesia in elderly patients. Time to initial response to verbal commands was the primary outcome measure. Therefore, there was no issue of test multiplicity. A power analysis was based on a previous study by Sakata et al. [8]. We estimated that the difference in means of recovery time would be 2.2 min (one-third of that which was observed in the referenced study) with a standard deviation of 2.0 min. Assuming an α of 0.05 (two-sided) and 80 % power, we calculated the sample size to be 15 in each group.

The data were expressed as mean ± standard deviation (SD) for continuous variables. Differences in patient demographics and other measurements except for the three recovery measures (i.e., the times to initial response, tracheal extubation, and leaving the OR) between control and treatment in each age group were analyzed using a Student's *t* test, a Mann–Whitney *U* test, and a Fisher's exact test. When analyzing the recovery measures, we used generalized pivotal methods, considering the fact that the recovery measures are essentially time-to-event measures that are likely to have a log-normal distribution, as indicated by Ledolter et al., in which the mean latency measured in minutes [Mean(X) such as the recovery measures in this present study depends on the following factors: $\text{Mean}(X) = \exp(\eta)$, where $\eta = \mu + 0.5\sigma^2$, and μ and σ^2 are the mean and variance of $\log(X)$] [11]. For comparing the recovery measures between control and treatment in each age group, a 95 % confidence interval (95 % CI) for the ratio of two means (treatment/control) and a *P* value were calculated using the generalized pivotal methods: $\text{Mean}_{\text{treatment}}/\text{Mean}_{\text{control}} = \exp(\eta_{\text{treatment}} - \eta_{\text{control}})$. A pivotal fixed-effects two-way analysis of variance (ANOVA) with two levels for the treatment factor (ANEclear) and two levels for the group factor (age) was performed to examine their interaction on the recovery measures. Nonlinear regression analysis was used to derive the time to reaching 50 % of the difference in BIS between at vaporizer shut-off and at extubation, which was defined as BIS ET_{50}. The BIS ET_{50} was statistically analyzed using the generalized pivotal methods as well as the recovery measures. The $EtCO_2$ and EtSevo values were plotted over time for each of the four groups. The statistical analysis was conducted using SPSS (version 20.0; SPSS, Chicago, IL, USA), R statistical software (version 2.15.2), and GraphPad Prism (version 3.0; GraphPad Software, San Diego, CA, USA).

Results

Patients' demographic data did not differ between control and treatment in each age group (Table 1). Mild hypercapnia with hyperventilation was accomplished using the device (Table 2). Anesthesia was maintained with comparable concentrations of sevoflurane in the elderly group, whereas inspired sevoflurane concentration in the middle-aged control group was slightly higher than that in the middle-aged treatment group (Table 2).

In the elderly group, the ANEclear significantly decreased all the recovery measures, because the 95 % CI of ratio of the means did not cover 1, with estimated decrease in mean time of 42.2 %, 40.5 %, or 28.7 %, respectively, for time to initial response, time to extubation, and time to leaving the OR. The ANEclear also significantly decreased all the recovery measures with estimated decrease in mean time of 28.3 %, 22.7 %, or 14.5 %, respectively, for time to initial response, time to extubation, and time to leaving the OR (Table 3). Table 4 shows the results of the pivotal fixed-effects two-way ANOVA with two levels for the treatment factor (ANEclear) and two levels for the group factor (age). The ANEclear-reducing effects on all the recovery measures did not reach significant interaction with patient age, suggesting that the recovery measures were shortened equally

Table 1 Patient characteristics, premedication, and duration of surgery and anesthesia

	Elderly			Middle-aged		
	Control	ANEclear	*P* value	Control	ANEclear	*P* value
Gender (M/F)	9/6	7/8	0.464	7/8	8/7	0.715
Age (years)	73.7 ± 5.4	69.0 ± 5.1	0.356	55.6 ± 5.8	57.2 ± 5.1	0.428
Height (cm)	153.1 ± 9.1	152.8 ± 11.4	0.951	159.7 ± 9.2	161.6 ± 10.8	0.520
Weight (kg)	56.4 ± 8.9	55.2 ± 8.7	0.708	62.3 ± 13.0	64.8 ± 11.9	0.692
BMI (kg/m^2)	24.0 ± 3.2	23.3 ± 2.4	0.636	24.3 ± 3.5	24.4 ± 3.1	0.899
Premedicated diazepam dose (mg)						
	4.3 ± 2.7	5.2 ± 2.7	0.234	9.1 ± 1.8	8.9 ± 2.0	0.936
Duration (min)						
Surgery	108.4 ± 38.0	125.9 ± 29.0	0.166	130.7 ± 33.7	129.5 ± 45.8	0.932
Anesthesia	157.1 ± 38.4	172.1 ± 29.5	0.241	174.1 ± 34.8	175.1 ± 45.6	0.943
Total dose of remifentanil (μg)						
	693 ± 162	760 ± 233	0.371	960 ± 547	1023 ± 457	0.539

Mean ± SD, *M* male, *F* female, *BMI* body mass index

Table 2 Respiratory data, bispectral index, and inspired and end-tidal sevoflurane concentration

	Elderly			Middle-aged		
	Control	ANEclear	*P* value	Control	ANEclear	*P* value
$EtCO_2$ (mmHg)						
At cessation of Sevo	33.1 ± 0.6	33.0 ± 0.7	0.771	32.9 ± 0.6	32.9 ± 0.5	0.757
At extubation	33.4 ± 1.3	45.1 ± 3.9	0.000	33.1 ± 0.9	46.2 ± 2.3	0.000
Minute ventilation (l/min)						
At cessation of Sevo	3.7 ± 0.7	3.5 ± 0.7	0.625	3.7 ± 0.7	4.1 ± 0.9	0.229
At extubation	3.8 ± 0.7	8.0 ± 1.2	0.000	3.9 ± 0.8	8.6 ± 1.1	0.000
BIS						
At cessation of Sevo	50.3 ± 7.5	50.5 ± 8.5	0.852	49.3 ± 9.7	47.9 ± 8.6	0.693
Insp Sevo (%)						
At cessation of Sevo	1.4 ± 0.1	1.4 ± 0.1	0.719	1.5 ± 0.1	1.4 ± 0.1	0.040
EtSevo (%)						
At cessation of Sevo	1.2 ± 0.1	1.3 ± 0.1	0.636	1.3 ± 0.1	1.3 ± 0.1	0.109
At extubation	0.1 ± 0.1	0.1 ± 0.1	0.204	0.2 ± 0.1	0.1 ± 0.1	0.051

Mean ± SD. *$EtCO_2$* end-tidal carbon dioxide, *Sevo* sevoflurane, *BIS* bispectral index, *Insp Sevo* inspired sevoflurane concentration, *EtSevo* end-tidal sevoflurane concentration

in both age groups (Table 4). The time-response curve of the BIS during emergence was statistically significantly shifted to the left with the ANEclear in each age group, as shown by estimated decrease in mean BIS ET_{50} of 45.3 % or 36.9 % in the elderly or middle-aged group, respectively (Fig. 2, Table 3). The ANEclear accelerated the estimated decrease in mean BIS ET_{50} equally in both age groups (Table 4).

Changes in $EtCO_2$ and EtSevo over time are shown in Fig. 3. Hyperventilation with the device increased $EtCO_2$ and decreased EtSevo in each age group compared with controls. Mean arterial pressure and heart rate were comparable during emergence, and there were no clinically significant differences in postanesthetic complications such as nausea and vomiting, excitement/delirium, shivering, or hypoxemia between with or without the ANEclear in each age group (Table 5).

Discussion

This study demonstrated that the use of hypercapnia in conjunction with hyperventilation, using the ANEclear anesthesia recovery device, accelerated recovery from sevoflurane anesthesia in elderly patients, as demonstrated by significant improvements in the time to initial response

Table 3 ANEclear-accelerating recovery times

	Control	ANEclear	$Mean_{ANEclear}/Mean_{control}$ (95 %CI)	*P* value
Initial response				
Elderly	9.8 ± 1.7	5.6 ± 1.0	0.576 (0.500, 0.660)	0.00000
Middle-aged	7.9 ± 2.2	5.7 ± 0.8	0.717 (0.591, 0.849)	0.00042
Extubation				
Elderly	10.6 ± 1.7	6.3 ± 0.9	0.595 (0.523, 0.673)	0.00000
Middle-aged	8.7 ± 2.2	6.3 ± 0.8	0.723 (0.609, 0.842)	0.00016
Leaving the OR				
Elderly	15.5 ± 2.8	11.0 ± 1.8	0.713 (0.622, 0.812)	0.00002
Middle-aged	12.6 ± 2.6	10.8 ± 1.5	0.855 (0.736, 0.982)	0.0269
BIS ET_{50}				
Elderly	8.8 ± 2.3	4.8 ± 1.1	0.547 (0.444, 0.663)	0.00000
Middle-aged	6.8 ± 2.6	4.4 ± 1.0	0.631 (0.463, 0.813)	0.00060

OR operating room, *BIS* ET_{50} time to reach 50 % of the difference between bispectral index measured at extubation and vaporizer shut-off

Table 4 Results of the fixed-effects two-way analysis of variance (ANOVA)

	Overall	ANEclear	Age	Interaction
Initial response	0.000001	0.000001	0.083141	0.060679
Extubation	0.000001	0.000001	0.075989	0.062534
Leaving the OR	0.000070	0.000025	0.022980	0.069215
BIS ET_{50}	0.000031	0.000014	0.057320	0.420061

OR operating room, *BIS* ET_{50} time to reach 50 % of the difference between bispectral index measured at extubation and vaporizer shut-off

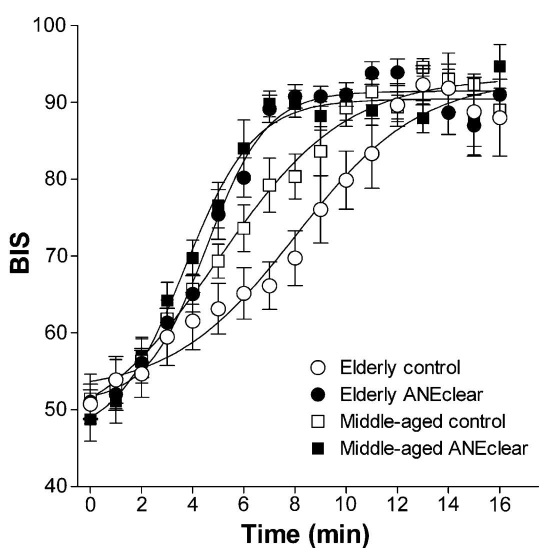

Fig. 2 Time-response curves of bispectral index (*BIS*). Mean ± SE

(the primary outcome measure), extubation, and leaving the OR versus controls. The acceleration in recovery accompanied by the corresponding changes in the BIS was comparable to that for middle-aged patients.

We statistically analyzed the recovery measures by using the generalized pivotal methods. Ledolter et al. [11] showed that the distributions of such recovery latencies measured in minutes are log normal, and the variances are substantially different between groups. Thus, they suggested that the generalized pivotal methods are a more appropriate method of analysis for studies of such measures. In this present study, the time to initial response without the ANEclear was age dependent [$Mean_{Elderly}/Mean_{Middle\text{-}aged}$ of the time to initial response without ANEclear: mean (95 % CI) = 1.238 (1.013, 1.479)], whereas the age-dependent difference was attenuated with ANEclear [$Mean_{Elderly}/Mean_{Middle\text{-}aged}$ with the ANEclear: mean (95 % CI) = 0.993 (0.874, 1.129)]. However, clearly, the ANEclear-reducing effects on recovery from sevoflurane anesthesia were comparable in both age groups according to the results of the pivotal fixed-effects two-way ANOVA, although the traditional ANOVA, if applied, would show the significant interaction between effects of the ANEclear and patient age for the time to initial response ($P = 0.017$).

The age-dependent delay in recovery from sevoflurane anesthesia without the device may be caused by age-related effects on both elimination and sensitivity to sevoflurane, as already described. Cortinez et al. [3] studied the influence of age on the relationship between end-tidal sevoflurane concentration and BIS. They found that the speed to offset of sevoflurane effect, as exhibited by BIS in elderly patients, was slower than that in the younger patients. The effect-site equilibration half-time at the age of 50 and 75 years was 2.1 and 2.78 min, respectively.

Sakata et al. [8] reported that the ANEclear (formerly the QED-100) reduced the time to eye-opening by 52 % in sevoflurane-anesthetized young patients undergoing elective surgery. In this present study, the time to initial

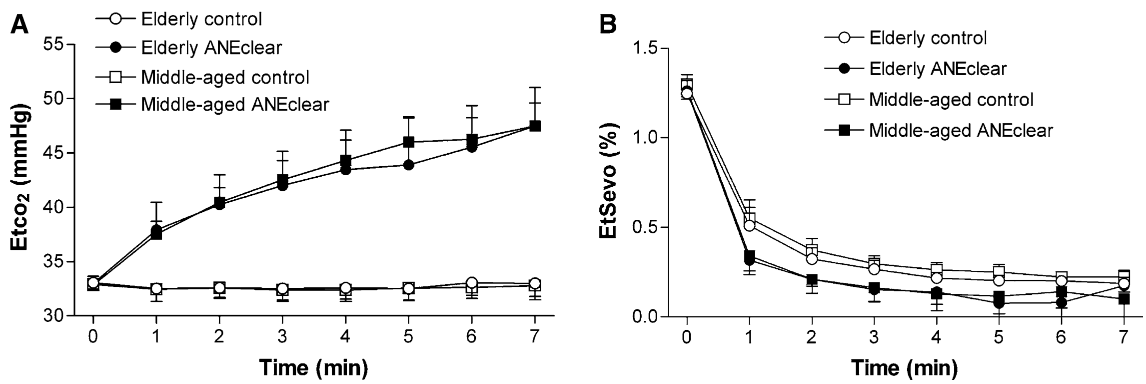

Fig. 3 Changes in end-tidal carbon dioxide (*$EtCO_2$*) and end-tidal sevoflurane (*EtSevo*) concentrations during recovery. Time *0* is cessation of sevoflurane

Table 5 Hemodynamic variables and complications during and after emergence

	Elderly			Middle-aged		
	Control	ANEclear	*P* value	Control	ANEclear	*P* value
Mean arterial pressure (mmHg)						
At cessation of Sevo	74.5 ± 9.1	77.1 ± 7.1	0.393	82.3 ± 16.3	75.1 ± 4.6	0.115
At extubation	109.9 ± 13.8	109.9 ± 20.2	0.100	110.7 ± 14.7	104.1 ± 13.7	0.214
Heart rates (bpm)						
At cessation of Sevo	57.3 ± 9.9	52.1 ± 8.0	0.130	60.2 ± 8.2	55.3 ± 8.5	0.116
At extubation	72.7 ± 14.5	73.1 ± 11.6	0.934	77.1 ± 11.6	73.7 ± 10.8	0.414
Postanesthetic complication (*n*)						
Nausea	0	0	–	2	1	0.500
Vomiting	0	0	–	0	0	–
Excitement/delirium	1	0	0.500	1	0	0.500
Shivering	1	0	0.500	0	0	–
Hypoxemia	0	0	–	0	0	–

Mean ± SD, *Sevo* sevoflurane

response was reduced by 42% or 28 % in the elderly or middle-aged group, respectively. This discrepancy could be explained by differences in study methods. Sakata et al. chose higher sevoflurane concentration (2 %) rather than that (1.5 %) in the present study, although the minimum alveolar concentration (MAC) of inhaled anesthetics decreases with increasing age; their sevoflurane concentrations correspond to 1.14 MAC, 0.93 MAC, or 0.86 MAC for the device group in the Sakata study and the elderly or middle-aged group in this present study, respectively [12, 13]. Sevoflurane has low solubility in plasma and therefore rapidly clears from the blood with normal ventilation. It is therefore possible that the ANEclear may be less effective when lower sevoflurane concentrations are used. In addition, function of the ANEclear is dependent on maximum alveolar ventilation and arterial CO_2. The minute ventilation of the study by Sakata et al. appeared to be higher (9.0 or 13.9 l/min in control or treatment group, respectively), which might cause the greater differences in the $EtCO_2$: 19.0, 11.7, or 13.1 mmHg for the Sakata study, and the elderly or middle-aged groups in this present study, respectively.

We chose ophthalmic surgery patients for several reasons. First, responses to surgical stress such as pain, inflammation, and fluid shifts may influence recovery time from general anesthesia [14–16]. Previous reports [16–18] suggest that ophthalmic surgery would be almost free of these stress responses when compared to major surgery, although surgical stress response was not measured in this present study. Second, relatively minimal stress response allows better standardization of anesthetic depth and opioid use between groups. Narcotics are associated with drowsiness after anesthesia [19]. The only narcotic used in this study was remifentanil, an ultra-short-acting opioid that was discontinued before the start of emergence. Third, ophthalmic surgeries are relatively consistent in terms of duration.

We kept $EtCO_2 \leq 55$ mmHg when using the ANEclear according to the previously reported methods for young and middle-aged patients [9]. Hypercapnia with $PaCO_2 \geq 100$ mmHg can impair level of consciousness and cause suppression of electroencephalogram during anesthesia, although Otten et al. indicated that such severe hypercapnia does not always lead to permanent neurological damage [20, 21]. In addition, cerebral edema and subarachnoidal hemorrhage as complications caused by hypercapnia have been reported, which is associated with hypercapnia-induced hypertension [20]. However, mild hypercapnia with $PaCO_2 = 55$ mmHg can lead to more favorable recovery from general anesthesia without any critical complications than normocapnia or hypocapnia in both young and elderly patients [10]. Collectively, $EtCO_2 \leq 55$ mmHg used in this present study may not be more harmful to elderly patients than young or middle-aged patients, although optimal arterial CO_2 tension to safely accelerate recovery from sevoflurane anesthesia in elderly patients remains unknown.

The ANEclear works according to the following theory. During recovery from inhaled anesthesia, alveolar concentration of anesthetic decreases in proportion to the volume of ventilation [22]. However, hyperventilation decreases $PaCO_2$, which decreases cerebral blood flow. Sasano et al. [6]. indicated that this phenomenon may reduce the anesthetic washout speed from the brain. Thus, shortening recovery time from inhaled anesthesia requires increasing the anesthetic washout speed from the brain and the lung simultaneously. Sasano et al. [6] added CO_2 to a breathing circuit to maintain $PaCO_2$ during hyperventilation. The ANEclear supplies CO_2 by allowing patients rebreathe their expired CO_2 with an expandable and contractible rebreathing loop, while a charcoal canister absorbs the volatile anesthetics to prevent their rebreathing (Fig. 1) [9].

Our study has several limitations. First, the anesthesiologist who performed the voice prompting and recorded the time when the patients initially showed an appropriate response was not blinded to the use of the device. The decision when to perform tracheal extubation was also based on the nonblinded anesthesiologist's clinical judgment. It is of note, however, that the BIS transitions during emergence were less subjective measures and showed significant differences between the control and ANEclear groups. Second, another potential limitation is that recovery was partly measured in terms of the time to eye opening, which may be more difficult after ophthalmic surgery than after other types of surgery [5, 9]. Other patient actions such as opening the mouth, nodding, and grasping hands were regarded as initial response when patients did not open their eyes to verbal command. Third, we used diazepam as a premedication in this study. It might have been more simple to evaluate the effects of the ANEclear on recovery time from sevoflurane anesthesia without such a sedative, although there was no significant difference in dose of diazepam between with and without the ANEclear in each age group. Finally, the choice of minimally invasive surgery to exclude the influence of surgical stress could be a study limitation in that it might make some differences between device and control patients difficult to detect. The clinical significance of the effects of hypercapnic hyperventilation might have been more pronounced if the study had included patients undergoing major surgery, as in the previous reports.

In conclusion, recovery time from sevoflurane anesthesia was decreased by the ANEclear anesthesia recovery device in the elderly group, and this reduction was comparable to that for middle-aged patients.

Acknowledgments The authors thank Dr. Derek Sakata, the Department of Anesthesiology, University of Utah, and Dr. Hiroshi Sasano, the Department of Anesthesiology and Resuscitology, Nagoya City University Medical School, for their helpful comments. The authors also thank the ophthalmologists for their cooperation. Moreover, the authors thank ACUMED (New York, NY, USA) for their editorial and statistical assistance.

References

1. Lerman J, Schmitt-Bantel BI, Gregory GA, Willis MM, Eger EI 2nd. Effect of age on the solubility of volatile anesthetics in human tissues. Anesthesiology. 1986;65:307–11.
2. Strum DP, Eger EI 2nd, Unadkat JD, Johnson BH, Carpenter RL. Age affects the pharmacokinetics of inhaled anesthetics in humans. Anesth Analg. 1991;73:310–8.
3. Cortinez LI, Troconiz IF, Fuentes R, Gambus P, Hsu YW, Altermatt F, Munoz HR. The influence of age on the dynamic relationship between end-tidal sevoflurane concentrations and bispectral index. Anesth Analg. 2008;107:1566–72.
4. Katznelson R, Van Rensburg A, Friedman Z, Wasowicz M, Djaiani GN, Fedorko L, Minkovich L, Fisher JA. Isocapnic hyperpnoea shortens postanesthetic care unit stay after isoflurane anesthesia. Anesth Analg. 2010;111:403–8.
5. Katznelson R, Minkovich L, Friedman Z, Fedorko L, Beattie WS, Fisher JA. Accelerated recovery from sevoflurane anesthesia with isocapnic hyperpnoea. Anesth Analg. 2008;106:486–91.
6. Sasano H, Vesely AE, Iscoe S, Tesler JC, Fisher JA. A simple apparatus for accelerating recovery from inhaled volatile anesthetics. Anesth Analg. 2001;93:1188–91.
7. Gopalakrishnan NA, Sakata DJ, Orr JA, McJames S, Westenskow DR. Hypercapnia shortens emergence time from inhaled anesthesia in pigs. Anesth Analg. 2007;104:815–21.
8. Sakata DJ, Gopalakrishnan NA, Orr JA, White JL, Westenskow DR. Rapid recovery from sevoflurane and desflurane with hypercapnia and hyperventilation. Anesth Analg. 2007;105:79–82.
9. Sakata DJ, Gopalakrishnan NA, Orr JA, White JL, Westenskow DR. Hypercapnic hyperventilation shortens emergence time from isoflurane anesthesia. Anesth Analg. 2007;104:587–91.
10. Hovorka J. Carbon dioxide homeostasis and recovery after general anaesthesia. Acta Anaesthesiol Scand. 1982;26:498–504.
11. Ledolter J, Dexter F, Epstein RH. Analysis of variance of communication latencies in anesthesia: comparing means of multiple log-normal distributions. Anesth Analg. 2011;113:888–96.

12. Eger EI 2nd. Age, minimum alveolar anesthetic concentration, and minimum alveolar anesthetic concentration-awake. Anesth Analg. 2001;93:947–53.
13. Mapleson WW. Effect of age on MAC in humans: a meta-analysis. Br J Anaesth. 1996;76:179–85.
14. Andrzejowski J, Sleigh JW, Johnson IA, Sikiotis L. The effect of intravenous epinephrine on the bispectral index and sedation. Anaesthesia. 2000;55:761–3.
15. Angel A. Central neuronal pathways and the process of anaesthesia. Br J Anaesth. 1993;71:148–63.
16. Desborough JP. The stress response to trauma and surgery. Br J Anaesth. 2000;85:109–17.
17. Barker JP, Vafidis GC, Robinson PN, Hall GM. Plasma catecholamine response to cataract surgery: a comparison between general and local anaesthesia. Anaesthesia. 1991;46:642–5.
18. Schwall B, Jakob W, Sessler DI, Taeger K, Frohlich D. Less adrenergic activation during cataract surgery with total intravenous than with local anesthesia. Acta Anaesthesiol Scand. 2000;44: 343–7.
19. Lichtor JL, Alessi R, Lane BS. Sleep tendency as a measure of recovery after drugs used for ambulatory surgery. Anesthesiology. 2002;96:878–83.
20. Otten M, Schwarte LA, Oosterhuis JW, Loer SA, Schober P. Hypercapnic coma due to spontaneous pneumothorax: case report and review of the literature. J Emerg Med. 2012;42:e1–6.
21. Yoshida H, Kushikata T, Kabara S, Takase H, Ishihara H, Hirota K. Flat electroencephalogram caused by carbon dioxide pneumoperitoneum. Anesth Analg. 2007;105:1749–52.
22. Stoelting RK, Eger EI 2nd. The effects of ventilation and anesthetic solubility on recovery from anesthesia: an in vivo and analog analysis before and after equilibrium. Anesthesiology. 1969;30:290–6.